Frequently asked questions

1. Why focus on a treatment when several vaccines are coming?

In November several vaccines, with better-than-expected potential efficacy, were announced by pharmaceutical companies. But these announcements do not mean that the pandemic will be under control soon.

First, universal access to these upcoming vaccines, especially in low-resource settings, may be slowed by vaccine nationalism and scalability challenges. Many high-income countries already pre-ordered massive quantities of doses and a potential risk with the first generation of vaccines is that their likely characteristics (requiring multiple doses, regular booster doses, and/or deep-freeze storage) could hinder rapid scale-up of coverage for people in resource-constrained settings.

Furthermore, there are still many unknowns about these announced vaccines and crucial information is still missing to evaluate their long-term protection efficacy, and their safety: how long does the immunity they provide will last; do they have the same efficiency for high-risk groups, such as the elderly or people with co-infections; will they be effective at preventing transmission too.

There is firm scientific consensus that both vaccines and treatments, together with diagnostics, are needed to respond effectively to COVID-19. No vaccine will fully suppress the need for therapeutic treatment: in disease control, treatment and prevention are always needed. There is also a low probability that any vaccine will be effective enough, and its coverage broad enough, to eliminate the incidence of new COVID-19 cases.

2. Why are trials needed for COVID-19 treatment in low- and middle-income countries?

The vast majority of COVID-19 clinical trials are being conducted in Europe, the US, and East Asia. Most trials are therefore testing treatments in contexts where doctors and nurses have considerable access to medical equipment and staff.

But hospital infrastructure in low-resource settings, notably in low- and middle-income countries, is highly limited compared to high-income countries. Intensive care unit capacity that has been so critical to the COVID-19 response (e.g. ventilators and supplemental oxygen) is particularly limited.

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2 See for example comprehensive data from World Bank and OECD:
   https://data.worldbank.org/indicator/SH.MED.BEDS.ZS
   https://data.oecd.org/healtheq/hospital-beds.htm

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It is therefore critical that:

- Health staff are able to treat COVID-19 before patients require hospitalization, in low-resource settings arguably even more so than in high-income settings; and
- Research protocols are designed to account for the specific needs and capacities of low-resource settings. Treatments that require constant refrigeration will be of little use in a region with unreliable access to electricity, as will treatments that require frequent blood tests, which are difficult to administer in regions suffering from an acute shortage of healthcare workers and laboratory capacity, for example.

If the needs and priorities of the most vulnerable populations are not taken into account in current research efforts against COVID-19, there is a risk that millions could be denied access to life-saving interventions.

3. Why is ANTICOV trial happening in Africa, despite the relatively low number of infections so far?

“We have fought a very good fight but the battle is not over. There is absolutely no room for complacency.”

Dr John Nkengasong, Director, Africa Centers for Disease Control – 2 November 2020

Of the 1,098 clinical studies on potential drugs underway around the world as of mid-September 2020, a mere 56 are being conducted on the African continent\(^3\). Of these, only a fraction are focused on identifying treatments for mild and moderate COVID-19 that are urgently needed for use in resource-constrained settings with very limited intensive care unit capacity.

Responses to drugs or vaccines can be influenced by, among other things, human genetics. Clinical trials in Africa, led by Africans, have a crucial role to play in identifying treatments adapted to Africa’s genetic diversity. Local leadership and participation in clinical research is also key to facilitating prompt adoption of new evidence into medical treatment guidelines, enabling faster access to new medical tools, and ensuring the trust of affected communities.

Although the epidemiological picture varies across the continent, data from the Africa CDC\(^4\) in early November have shown a 15% increase in the number of weekly new cases of COVID-19. While Africa has largely avoided the large-scale mortality from COVID-19 seen in other parts of the world, as of 10 November 2020, 15 countries are reporting case fatality rates that are higher than the global case fatality rate of 2.5%.

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African leaders’ timely and concerted response to COVID-19 has undoubtedly contributed to the region’s relatively low cumulative case count – just 4% of total cases reported globally. However, there is currently no scientific consensus on which other factors may have played a role in limiting transmission or individual risk of infection.

The African medical and scientific community continue to advise caution, particularly as lockdowns end and borders open in many countries. The risk remains that a second, more serious wave could follow in the months ahead, as it is already the case in countries like Kenya.

Identifying early treatments that can prevent progression of COVID-19 to severe disease is critical to ensuring countries are prepared to respond. In addition to reducing morbidity and mortality, effective treatments that also help to limit transmission could reduce the economic impact of additional lockdowns, which have shown to be devastating for households and communities that rely on daily wages.

4. Why is ANTICOV focusing on mild-to-moderate cases?

“Treating patients suffering from mild forms of the COVID-19 infection before they evolve into more severe disease and require hospitalization is a critical challenge around the world. This is even more important in resource-limited healthcare settings of low- and middle-income countries. The ANTICOV trial is designed with this objective in mind, aiming to find safe and effective treatments that work for everyone.”

Dr Nick Cammack, COVID-19 Therapeutics Accelerator Lead, Wellcome

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The SARS-CoV-2 infection can be roughly divided into two stages: a first, viral stage, with an asymptomatic incubation period, followed by the development of mild-to-moderate symptoms; and a second, an inflammatory stage, with more severe symptoms and in some patients an excessive inflammatory response from the immune system.

Most of the clinical trials being carried out worldwide are focusing on severe, hospitalized patients. There is an urgent need to evaluate treatment for mild-to-moderate cases – both to halt onward disease transmission and to stop the progression of the disease to more severe forms.

In low- and middle-income countries, identifying these treatments is an urgent public health imperative: a significant proportion of patients with mild-to-moderate symptoms will become seriously ill and require hospitalization. Many health systems on the African continent are fragile and could be rapidly overwhelmed by spikes in cases of severe COVID-19.

5. How does ANTICOV fit in with the global COVID-19 R&D response?

The ANTICOV trial is complementary to other clinical trials on therapeutics for COVID-19. This includes:

- **SOLIDARITY**, launched by the WHO in March 2020, which focuses on moderate-to-severe hospitalized cases, to prevent these patients from dying. SOLIDARITY is a large-scale randomized trial that started with four treatment options – including hydroxychloroquine (since dropped) and lopinavir/ritonavir – compared against the standard of care. The ANTICOV study is tackling the problem earlier, looking at solutions that would prevent mild and moderate cases from becoming severe. Patients in the ANTICOV trial whose symptoms become severe will be referred to the SOLIDARITY trial if relevant and appropriate.

- The **COVID-19 Therapeutics Accelerator**, which targets different populations. ANTICOV focuses on LMICs, while the Therapeutics Accelerator carries out two trials in high-income countries: one to find treatment for severely ill patients, the other for mild to moderately ill patients. The Therapeutics Accelerator is initiated and funded by the Bill & Melinda Gates Foundation, Wellcome, and Mastercard. The ANTICOV consortium will notably collaborate with the Accelerator to support the identification of new treatment candidates.

The ANTICOV study also fits with the **Access to COVID-19 Tool (ACT) Accelerator**, which was launched in April 2020 by the WHO to ensure equitable global access to innovative tools for COVID-19 for all. Unitaid – one of the principal funders of ANTICOV – is a co-convenor of Therapeutics Partnership of the Accelerator.

ANTICOV investigators will publicly share their protocols, study documents, research data and results, according to the principles of open science. This approach is essential to accelerate research and find
answers as soon as possible. The ANTICOV consortium is also working closely with the WHO to share its data and help the organization to provide adequate guidance.

6. Why is ANTICOV focusing initially on “repurposed” drugs?

ANTICOV researchers are seeking to develop therapeutic solutions as quickly as possible. One of the most effective and widely accepted strategies to compress long R&D timelines is to evaluate whether existing drugs, about which detailed safety information is already known, could be useful in treating other diseases. This is known as “drug repurposing”.

“Repurposed” drug candidates are existing drugs that are already registered for one or more diseases or indications and which are tested for efficacy against a new indication – in this case COVID-19. They are known to be safe at specific doses, and clinicians and doctors are familiar with how to use them. Should ANTICOV trial results demonstrate that these medicines are efficacious against COVID-19, they will be accessible very quickly as they are already manufactured at scale. An added benefit is that many are off-patent and therefore produced by generic companies, which means they are more likely to be affordable.

As an adaptive platform clinical trial, ANTICOV allows for rapid decisions to be made as the trial progresses, including adding, continuing, or stopping treatment arms based on an ongoing analysis of results. While working to assess additional repurposed drug candidates for potential inclusion in the trial, the ANTICOV consortium is also actively engaged in identifying the most promising drug candidates emerging from pre-clinical and early clinical research that may be efficacious for treatment of mild-to-moderate COVID-19.

7. Which drugs will be tested by ANTICOV?

The ANTICOV trial is designed to test not one, but several therapeutic options.

The first trial arms will be dedicated to provide guidance on the efficacy of the current standard of care in African countries. But ANTICOV will also serve as a platform able to continuously test therapeutic solutions that emerge from global research efforts.

ANTICOV is an “adaptive platform” trial. This means it can respond very quickly to results and keep abreast of the latest science:

- If an analysis reveals that the efficacy of any treatment included in ANTICOV is low compared to the control arm, it can be removed from the trial rapidly; and
- If a new potential COVID-19 treatment for mild-to-moderate cases shows promise in pre-clinical studies, it can be added to the trial rapidly.

A number of different therapeutic options that could be included in ANTICOV are currently being evaluated. In addition, the trial will seek to provide definitive evidence on the use of hydroxychloroquine and lopinavir/ritonavir in mild and moderate cases.
7.1 What are the promising drugs that will be included in ANTICOV?

With new evidence and knowledge on COVID-19 being generated extremely rapidly, ANTICOV researchers are actively looking to integrate other promising drugs into the study with new study arms. The ANTICOV Consortium is working with organizations conducting screening and repurposing efforts for SARS-CoV-2 to share information, avoid duplication of efforts, and ultimately include the most promising candidates in the ANTICOV trial.

The ANTICOV trial works in close collaboration with the Unitaid-led Access to COVID-19 Tools Accelerator (ACT-A) and its Therapeutics Partnership. The ACT-A Therapeutics Partnership is co-convened by Wellcome, on behalf of the COVID-19 Therapeutics Accelerator, and Unitaid, one of the principal funders of ANTICOV. The ANTICOV consortium’s selection of trial drugs is informed by reviews conducted by the ACT-A Therapeutics Partnership expert working group identifying new treatment candidates, with leadership from Wellcome and the Bill & Melinda Gates Foundation. Wellcome is also exploring opportunities to support DNDi and partners’ work to design and implement a translational platform for mild and moderate COVID-19 that aims to identify promising new chemical entities and transition successful candidates into clinical trials.

In June 2020, DNDi organized an online conference with 11 global health organizations, including the World Health Organization (WHO), Bill & Melinda Gates Medical Research Institute, Wellcome, the National Institutes of Health, Medicines for Malaria Venture, Unitaid, INSERM and other academic groups to identify a number of promising drug candidates for mild and moderate COVID-19 cases and offer recommendations about the treatments to be included in the future arms of ANTICOV.

Experts conducted an evaluation of the available data and evidence and looked at many different factors, including the safety, cost, and accessibility of these drug candidates. Leading combinations were selected to be evaluated pre-clinically. Results are expected by mid-November. New regimens would be added to ANTICOV as soon as possible thereafter. One strong contender for inclusion (although this remains to be confirmed) is the oral combination of nitazoxanide and atazanavir/ritonavir, drugs with different mechanisms of action, which could answer to the need to ensure rapid exposure to drug concentrations associated with antiviral efficacy.

In the meantime, the initiation of ANTICOV with the first two study arms (hydroxychloroquine and lopinavir/ritonavir, see below) will not only provide meaningful results, but will prepare all study partners to ensure capacity is in place for the next arms to be added.

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5 https://unitaid.org/covid-19/act-accelerator/#en
6 https://www.therapeuticsaccelerator.org
7.2 Why is hydroxychloroquine included in ANTICOV?

*In vitro* data show that chloroquine (CQ) and hydroxychloroquine (HCQ) are active against SARS-CoV-2 infection. However, *in vitro* activity in the laboratory does not necessarily translate into efficacy in humans, so clinical trials are needed.

Like all drugs, HCQ could have differing efficacy against COVID-19 according to the stage of the disease or to the SARS-CoV-2 viral load of the patient when it is first administered. Several large, randomized trials have shown a lack of efficacy of HCQ as a treatment for COVID-19 in severely ill hospitalized patients, but the drug still needs to be tested in large, randomized controlled trials with mild and moderate cases. A small number of randomized controlled trials of HCQ for mild and moderate cases have been conducted; however, they do not share a common approach to measuring treatment efficacy and are insufficient to provide conclusive guidance to shape treatment guidelines.

> “What is clear now is hydroxychloroquine does not have an impact on the disease course on mortality in hospitalized COVID-19 patients. Where there is still a gap is: does it have any role at all in prevention or minimizing the severity of the illness in early infection. We need to complete those large trials to have a definitive answer on that.”

**Dr Soumya Swaminathan**, Chief Scientist, World Health Organization – 18 June 2020

Providing robust, science-based evidence on HCQ is urgently needed to inform policy decisions. Today, at least 16 African countries (including 7 of the 13 ANTICOV countries) are recommending the use of CQ or HCQ, even though scientific evidence is lacking. HCQ is being tested in ANTICOV in accordance with the research priorities of our African partners and the needs of African doctors and scientists calling for decisive data to help confirm or inform the standard of care.

The safety of CQ/HCQ is well established for the treatment of malaria and autoimmune disease. Three earlier randomized controlled trials investigating HCQ in outpatients (as pre-exposure prophylaxis, post-exposure prophylaxis, and early treatment for COVID-19) found that randomized clinical trials can safely investigate whether hydroxychloroquine is efficacious for COVID-19, with data demonstrating that gastrointestinal side effects were common but mild, while serious side effects were rare.

7.3 Why is lopinavir/ritonavir included in ANTICOV?

ANTICOV is exploring a dose regimen of the lopinavir/ritonavir (LPV/r) combination that has not been tested in other trials in order to determine if LPV/r is effective in the treatment of mild-to-moderate cases of COVID-19, before the inflammatory stage of the disease is reached. A stronger initial ‘loading

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7 [https://www.nature.com/articles/s41422-020-0282-0](https://www.nature.com/articles/s41422-020-0282-0)

8 [https://www.nature.com/articles/s41421-020-0156-0](https://www.nature.com/articles/s41421-020-0156-0)


9 [https://www.medrxiv.org/content/10.1101/2020.07.16.20155531v3](https://www.medrxiv.org/content/10.1101/2020.07.16.20155531v3)
dose’ of the combination will be used to assess whether reaching higher therapeutic concentrations earlier could be beneficial.

Various studies (including **RECOVERY**, **SOLIDARITY**, and **LOTUS**) have concluded that LPV/r therapy has no efficacy for severe and hospitalized cases. WHO highlighted that its decision to discontinue the LPV/r arm of its SOLIDARITY trial applies only to severe cases and “does not affect the possible evaluation in other studies of … lopinavir/ritonavir in non-hospitalized patients or as pre- or post-exposure prophylaxis for COVID-19.” There are currently no data available from large clinical trials testing LPV/r in the early stage of COVID-19, although results are expected soon.

Lopinavir and ritonavir are antiretroviral drugs widely used in combination for the treatment of HIV as currently recommended by WHO for second-line HIV treatment (i.e. following failure of initial treatment). Half a million people use the combination globally and its safety and side-effects are well established. LPV/r is off-patent and multiple affordable generic sources exist.

8. **How will ANTICOV ensure best practice in ethics?**

The ANTICOV clinical trial is designed to meet the specific needs of African communities. The trial is carried out by African scientists and is approved by the national ethics, regulatory committees, and health ministries of each study country.

Ethics and regulatory committees in each study country assess whether local communities will benefit from the research, and would therefore only approve a trial for a medicine that would ultimately be easily accessible by the communities that contributed to developing it.

ANTICOV has been reviewed with support from the **African Vaccine Regulatory Forum (AVAREF)**. WHO established AVAREF in 2006 to build the capacity of regulatory and ethics agencies and improve harmonisation of practices across African countries. AVAREF is made up of representatives from African ethics and regulatory review bodies and was recently mandated to expedite clinical trial reviews for COVID-19.

The ANTICOV trial respects the most stringent ethical standards: no participant can be enrolled without first giving their informed consent; the personal data of all participants is kept confidential; participants can leave the trial at any time; and assistance will be provided to participants should any issue arise because of the trial.

DNDi, which is coordinating ANTICOV, has a long track record of championing African-led clinical research, from the development of the **first all-oral treatment for sleeping sickness** with the close cooperation of countries like the Democratic Republic of Congo, to the set-up of regional clinical

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11. [https://www.ft.com/content/5a7a9658-6d1f-11ea-89df-41bea055720b](https://www.ft.com/content/5a7a9658-6d1f-11ea-89df-41bea055720b)

12. See for example this interview of Dr Aissatou Touré, member of the COVID-19 Clinical Research Coalition Ethics Working Group: [https://www.youtube.com/watch?v=wm2ok-x-vfc](https://www.youtube.com/watch?v=wm2ok-x-vfc)
research platforms in Africa for sleeping sickness and leishmaniasis. All of these initiatives are led by African researchers and scientists with the strong support of their governments.

ANTICOV also includes excellent African clinical research organizations, such as Kenya’s KEMRI, Ethiopia’s University of Gondar, and Ghana’s KCCR, to name only a few.

9. Why have some countries started the ANTICOV trial, while others haven’t? When will they be ready?

Approvals from health authorities and national ethics committees are required in each ANTICOV country. These approvals are essential, and some take more time than others.